REMARKS

Reconsideration of the rejection of all claims is respectfully requested in view of the above amendments and the following remarks.

As detailed further below, all claims have been canceled except for independent claims 51 and 52 in order to simplify and focus the prosecution of this application on the multi-step integrated process of amended claims 51 and 52. Claims 51 and 52 have also been amended to address the apparent misunderstanding that all Applicants have done is to "operate a process continuously," which the Examiner repeats several time throughout the final rejection. As explained further below, applicants have not taken a known process and made it continuous. Rather, Applicants have developed and presently claim an integrated multi-step batch process that allows a substantial reduction in the number of intermediates that must be isolated, and yet allows final product to be made in high quality and yield on a large scale (specification page 2, lines 7-14). The presently claimed process is in particular an improvement over the prior art process for making the compound of formula I disclosed in WO 96/33980 as discussed at pages 1 and 2 of the present specification, and it is respectfully submitted that none of the additional references applied by the Examiner in this Action, individually or taken together, render obvious the integrated multi-step batch process as presently claimed.

Claim Amendments

Claims 1, 4-8 and 30-50 are *newly* cancelled above (all of claims 1-50 now being cancelled) in order to focus the prosecution of this application on the overall integrated process of claims 51 and 52, so as to place this application in condition for allowance or in better condition for appeal.

Claim 51 has been amended to correct the typographical error noted by the Examiner, changing the erroneous reference to "Formula H" to correctly read "Formula II."

Claims 51 and 52 are directed toward preferred embodiments of the total integrated process from the starting compound of Formula III through to the desired compound of Formula II. These claims have been amended above to complete the

process sequence to include specific recitation of the formation of the compound of Formula II in cyclisation step (c), and its precipitation in solid form upon cooling with optional separation by filtration. Support for the temperature range recited in step (c) of claim 52 is found, *inter alia*, at specification page 4, lines 25-28, and support for the additional recitations on the formation and precipitation of the compound of Formula II in step (c) of claims 51 and 52 is found in the specification in Example 1, specifically at page 11, lines 16-18.

Claims 51 and 52 have also been amended to address and hopefully clarify the apparent misunderstanding that all Applicants have done is to "operate a process continuously," which the Examiner repeats several time throughout the rejection. As explained further below, applicants have not taken a known process and made it continuous. Rather, as described in the specification and clarified in amended claims 51 and 52, Applicants have developed the presently claimed procedures and conditions whereby three main reactions have been incorporated into a single integrated multi-step batch process for preparing the compound of Formula II starting with the compound of Formula III, while avoiding the need for isolation or other purification of intermediates *per se* during the process. Thus, the claims have been amended to make more clear that reduction step (a) is carried out in an aqueous phase, and that the organic phase comprising compound of Formula IV that is extracted from step (a) is subjected to hydration in step (b); that the reaction mixture comprising the compound of Formula V formed in step (b) is subjected to the cyclisation of step (c); and that after cyclisation the compound of Formula II precipitates upon cooling from the solution formed in step (c), and optionally is removed by filtration. Claim 52 adds to claim 51 the recitation of more specific and preferred reagents, solvents, catalysts and/or reaction conditions. Support for this additional clarification of claims 51 and 52 is found, *inter alia*, in Example 1.

In short, it is believed that these amendments make clearer that there is no isolation of any intermediate as such throughout this multi-step fully integrated batch process.

It should be clear from the above that these amendments are supported by the specification and claims as filed and no new matter is being added. Therefore, entry of

these amendments is believed to be appropriate and is respectfully requested. These amendments are made without waiver or prejudice to Applicants' right to prosecute any subject matter deleted thereby in one or more continuing applications.

Following entry of these amendments, claims 51 and 52 are pending in this application.

Claim Objections

The objection to claim 45 has been obviated by the cancellation of that claim, and the objection to claim 51 has been overcome by the above correction to claim 51.

Claim Rejections - 35 USC § 103 and Examiner's Response to Amendments and Arguments

All claims remain rejected under 35 U.S.C. § 103(a) as being unpatentable over US Patent No. 6,294,532 (hereinafter "US '532" in combination with JP 11228515 (hereinafter "JP '515") and WO 02/00649 (hereinafter "WO '649"), for the identical reasons and assertions stated in the previous Action mailed February 13, 2008. Applicants fully responded to this ground for rejection by the Amendments and Response filed August 13, 2008 in a manner that was believed to overcome this rejection. However, the Examiner has disagreed and has repeated this same rejection in the present Action.

Applicants and the undersigned appreciate the Examiner's extensive Response to Amendment and Arguments set forth at pages 2-4 of the present Action, which helps to clarify and focus the remaining issues. Therefore these Remarks will begin by commenting on the Examiner's Response to Applicants' previous amendments and arguments.

First, there appears to be a fundamental misunderstanding that forms the basis for several of the points made in the Examiner's Response, and therefore this will be addressed first. Specifically, the Examiner repeatedly asserts as a basis for obviousness that it is well within the expected skill of the practitioner to "*operate a process continuously*":

> For the claims that exclude isolation, it is well within the expected skill of the practitioner to operate a process continuously.

(Action at page 3, lines 13-14).

> Applicants' argue that there is no disclosure in the prior art references that the Formula's IV and V can be taken from their preparation and introduced into the next step in a solution of an organic solvent. Again, this argument is not persuasive as it is well within the expected skill of the practitioner to operate a process continuously.

(Action at page 3, lines 17-20)

> In regards to the requirement to exclude isolation steps in some claims, it is noted that it is well within the expected skill of the practitioner to operate a process continuously.

(Action at page 4, lines 1-3).

However, applicants are not claiming a "continuous" process, and have not argued "continuous" as a distinction over the prior art. A continuous process is one wherein reactants are continuously feed into the process apparatus and product is continuously produced and removed from the process apparatus. In contrast, in a batch process a discrete quantity of reactants is introduced and processed to produce a discrete batch of product, which batch process may be repeated by starting with another discrete quantity of reactants to produce a further batch of product, *etc*.

A "continuous process" involving multiple process steps can, and generally does, involve the separation and isolation of intermediates along the way so as to get rid of potentially troublesome reaction by-products, impurities, unreacted reactants, catalysts, solvents and the like that may interfere with subsequent reactions and/or the isolation and purification of the final product. Similarly, a "batch" process involving multiple process steps can, and generally does, involve the separation and washing of intermediates before they are introduced into the next step of the batch process, again with the objective of getting rid of potentially troublesome reaction by-products etc. that may interfere with subsequent process steps.

The objective, and a unique and unobvious feature, of Applicants' claimed process is that several different reactions in this multi-step process have been integrated in a manner such that the intermediate compounds produced by those reactions need not

be (and are not) isolated as such before being introduced into the next reaction step, *i.e.*, the intermediates need not be separated and/or purified from all other reactants, by-products, impurities etc. of the previous reaction step before being reacted to the next intermediate or product compound. Whether or not these integrated process steps are performed in a batch or continuous manner is not a feature of the invention. In fact, claimed process is carried out as a batch operation rather than as a continuous process, wherein a discrete quantity of the compound of Formula III is processed through the integrated process sequence to produce a batch of the compound of Formula II. See, *e.g.*, the process of Example 1.

The above amendments to the claims have been made to clarify and accentuate this unique and unobvious feature of the presently claimed process. Thus, referring to claims 51 and 52, the process has been more specifically characterized at the outset of the claims as a "multi-step batch process," with support from, *inter alia*, Example 1. Step (a) is carried out in an aqueous slurry of the compound of Formula III in the presence of a water-soluble inorganic reducing agent. The compound of Formula IV thus formed is not isolated as such from the reaction mixture, but an organic phase comprising the compound of Formula IV is separated from the aqueous phase by extraction with an organic solvent. This organic phase comprising the compound of Formula IV as well as any other organic reactants, by-products and impurities is added to a polar protic solvent, and organic extracting solvent is removed by distillation. The resultant solution, still comprising the intermediate of Formula IV and other organic components from the reaction mixture, in said polar protic solvent is subjected to the hydration of step (b).

In step (b) the compound of Formula IV contained in the resultant solution from step (a) is reacted in the presence of an alkali metal base and in a polar protic solvent to form a reaction mixture comprising the compound of Formula V. This reaction mixture comprising the compound of Formula V and whatever else remains in, or has been formed in, the reaction mixture, is subjected to the cyclisation reaction of step (c). This reaction mixture from step (b) is acidified with formic acid and concentrated by distillation, and excess formamide is added as both a reactant and a solvent. The resultant solution is maintained at elevated temperature to form the compound of Formula II,

which precipitates from the resultant solution upon cooling and optionally is removed by filtration. Again, claim 52 adds to claim 51 the recitation of more specific and preferred reagents, solvents, catalyst and/or reaction conditions.

The invention as claimed in claims 51 and 52, therefore, is not operating "a process continuously", as the Examiner has asserted. Moreover, the presently claimed invention is not simply combining separate process steps from the applied references, even if there were some motivation to do so. Thus, it should clear from the above that the presently claimed invention is not simply taking isolated compound of Formula IV from step (a) and introducing it into step (b); and is not simply taking isolated compound of Formula V from step (b) and introducing it into step (c), as the Examiner seems to be implying.

Addressing the remainder of the Examiner's Response to Amendment and Arguments:

- At page 2 of the Action, the Examiner comments:

> In regards to the 35 USC 103(a) rejection, Applicants argue that the Examiner has used impermissible hindsight. This argument is not persuasive as it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See In re McLaughlin, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

This statement from *In re McLaughlin* simply observes that the *reasoning* involved in a judgment of obviousness must necessarily be made from the past or hindsight perspective of the person of ordinary skill in the art at the time of Applicants' invention. However, as the Court in *McLaughlin* observed, as well as every Federal Circuit decision addressing "hindsight," this *reasoning* must take into account only *knowledge* which was within the level of ordinary skill at the time the claimed invention was made. Thus the *improper* "hindsight" that must be avoided in an obviousness evaluation is the use of *knowledge or guidance* that was not in the prior art, but rather was gleaned from Applicants' disclosure. Applicants' assertion of improper hindsight in

this application is based on the Examiner's use of *knowledge* gleaned only from Applicants' disclosure in guiding the selection of these particular references and the selection of these particular process steps from the myriads of available alternatives, to combine in attempting to piece together Applicants' presently claimed invention. Nevertheless, their combination as suggested by the Examiner would not achieve Applicants' presently claimed invention.

- At page 2 of the Action, the Examiner comments:

> Applicants argue that the claimed process provides significant advantages of reduced time and cost particularly in large scale commercial production. This argument is not persuasive as an Attorney's arguments of unexpected results cannot talke the place of evidence in the record.

(Action at page 2).

It is respectfully pointed out that the above statement referred to by the Examiner (from pages 9-10 of Applicants' August 13, 2008 response) is *not* "Attorney's argument" but rather closely paraphrases the passage from Applicants' specification at page 2, lines 7-14, which passage is fully quoted at page 10 of that response. Moreover, the statement and supporting quotation were *not* presented to assert "unexpected results" but rather were presented to observe that *none* of the prior art references disclose or suggest the integrated process as presently claimed, which is suitable for large scale manufacture without isolation of intermediates. It is therefore Applicants' position that the applied references do not give rise to *prima facie* obviousness, but that Applicants' claimed integrated process is itself unobvious over these references and the state of the art as a whole at the time of Applicants' invention, as discussed further below.

- At pages 2-3 of the Action, the Examiner further comments:

> Applicants argue that the Examiner's statement that "since each step of the process appears to be relatively complete in itself and there is no indication of an interaction between steps" is not accurate with respect to the new claims. This argument is not persuasive as the statement by the Examiner is that "since each step of the process appears to be relatively complete in itself and there is no indication of an interaction between steps of such a type that would lead one of ordinary skill in the art to doubt that a substitution of alternative steps known to the art could be made." The Examiner has concluded that there is no indication of an interaction between the steps of such a type that would lead one of ordinary skill in

> the art to doubt that a substitution of alternative steps known in the art could be made. The examiner has not concluded that there is no interaction between steps, but that there is no interaction that would lead one to doubt that alternative steps could be made.

The undersigned stands corrected, and now appreciates that the Examiner was not asserting there was no indication of an interaction between steps of Applicants' process, but rather was saying that there was no indication of an interaction between steps "of such a type that would lead one of ordinary skill in the art to doubt that a substitution of alternative steps known in the art could be made." Nevertheless, it is respectfully submitted that there is no teaching or suggestion in the art that *would lead* such skilled person to *select these particular portions* of *these particular references* to be combined in the first place, without the guidance of Applicants' present disclosure, and *even if* one had serendipitously made these multiple selections, they would not in any event have achieved the invention of Applicants' claims 51 or 52, as discussed further below.

- At page 3 of the Action, the Examiner further comments:

> Applicants' argue that there is no need in the claimed invention to isolate Formula IV or V. This argument is not persuasive as for some claims, such as claim 1, isolation is not an excluded claim limitation. For the claims that exclude isolation, it is well within the expected skill of the practitioner to operate a process continuously.

Claim 1 has been cancelled, and remaining claims 51 and 52 *do not permit isolation* as such of the compounds of Formula IV or V. Specifically, it is recited in step (a) that "the compound of Formula IV so formed is not isolated as such ... and the resultant solution of the intermediate of Formula IV in said [polar protic solvent] is used in the hydration of step (b);" and step (b) provides "the compound of formula V so formed is not isolated as such but is prepared and used in the cyclisation reaction of step (c) as a solution in [said polar protic solvent]." Claims 51 and 52 have been amended herein to further clarify that there is no isolation of the intermediates *per se* between the process steps.

The Examiner's further comment that "it is well within the expected skill of the practitioner to operate a process continuously" was addressed above, and is not here

applicable.

- At page 3 of the Action, the Examiner comments:

> Applicants' discusses the wastefulness of the process of WO 96/33980, however, this reference was not applied against applicant.

Whether or not the Examiner has applied the process of WO 96/33980 against the presently claimed invention, it is still a part of the state of the relevant art at the time of Applicants' invention. As the Examiner is aware, *all* the relevant art must be considered as a whole when making an assertion of obviousness. It is inappropriate to pick and chose references or portions thereof that support an obviousness rejection while ignoring those references or portions thereof that may contradict the rejection.

- At page 3 of the Action, the Examiner comments:

> Applicants' argue that there is no disclosure in the prior art references that the Formula's IV and V can be taken from their preparation and introduced into the next step in a solution of an organic solvent. Again, this argument is not persuasive as it is well within the expected skill of the practitioner to operate a process continuously.

Again, the Examiner's comment that "it is well within the expected skill of the practitioner to operate a process continuously" was addressed above, and is not here applicable.

- At page 4 of the Action, the Examiner further comments:

> In regards to the requirement to exclude isolation steps in some claims, it is noted that it is well within the expected skill of the practitioner to operate a process continuously. In regards to step (a) in the new claims, it is noted that the prior art reference WO 02100649 discloses the use of a water soluble inorganic reducing agent sodium hydrosulfite which is another name for sodium dithionite. Also, WO 02100649 discloses extraction with an organic solvent of methylene chloride. WO 02100649 also discloses the polar protic solvent of water. While some of Applicants' claims include tert-amyl alcohol as the polar protic solvent in steps (a), (b) and (c), it is noted that the prior art references all disclose polar protic solvents, in particular, water, methanol and formic acid. However, the Courts have decided per In re Boesch, 205 USPQ 215 (1980), that the optimization of variables in a known process is prima facie obvious. Therefore, the claimed process would have been suggested to one skilled in the art. While JP'515 discloses calcium carbonate as the alkali metal

> base, it is again noted that optimization of variables in a known process is prima facie obvious.

Again, the Examiner's comment that "it is well within the expected skill of the practitioner to operate a process continuously" was addressed above, and is not here applicable.

With reference to WO 02/00649 (it is presumed this is what the Examiner is referring to as "WO 02100649" in the above passage), Applicants agree that this document refers to the water soluble inorganic reducing agent sodium hydrosulfite (sodium dithionite), and disclose extraction with an organic solvent of methylene chloride. It is presumed that the Examiner is referring General Scheme 2 at page 77 of this document, and specifically to the description under "Compound H" at page 78, lines 25-32. However, it is particularly noteworthy that the "residue was purified by silica gel chromatography ... to give the title compound" (emphasis added), which *supports* Applicants' argument of non-obviousness of the presently claimed invention.[1]

It is thus respectfully submitted that *even if* the skilled person were somehow motivated (without use of hindsight of Applicants' present disclosure) to combine the teachings of US '532 with JP '515 and WO '649, they would not, in any event, achieve the process of Applicants' presently claimed invention. JP '515, which is said to correspond to Applicants' steps (a) and (b), carries out the reduction step by hydrogenation using a palladium catalyst. In contrast, the reduction step of both claims 51 and 52 carries out the reduction in an *aqueous* medium in the presence of a water-soluble inorganic reducing agent (for whatever reason -- perhaps a concern over the industrial use of highly explosive hydrogen). JP '515 therefore does not need (or disclose) an extraction step from the aqueous medium using an organic solvent (such as

[1] Treatment with sodium hydrosulfite is also referred to at page 140, line 20, followed extraction with ethylacetate. Although the intermediate from this step does not appear to be isolated *per se* at this point, it is noted that in a following step the intermediate is purified by silicagell chromatography (page 141, line 9). Treatment with sodium hydrosulfite is also referred to at page 149, line 6, followed by extraction with methylene chloride. Again, although the intermediate from this step does not appear to be isolated *per se* at this point, the residue in the subsequent step is "triturated with ether to give title compound as a yellow solid," *e.g.*, a purification/isolation step. This disclosure supports, if anything, the *non*-obviousness of Applicants' presently claimed process.

methylene chloride). The Examiner cites WO '649 as disclosing the use of a water soluble inorganic reducing agent sodium hydrosulfite (sodium dithionite), and also as disclosing extraction with an organic solvent of methylene chloride. However, as discussed above, in each instance where sodium hydrosulfite is used in WO '649, the intermediate of that step or in close succeeding step is isolated and/or purified by chromatography or trituration, which intermediate isolation or purification step is specifically excluded by the objective of the present invention *and the express wording of claims 51 and 52*. Thus, there is no teaching by any combination of these references of Applicants' presently claims steps (a) and (b), and there is nothing in US '532 (cited as corresponding to Applicants' step (c)) that in any way remedies this deficiency.

Accordingly, it is respectfully submitted that the invention as presently claimed is not rendered obvious by any combination of the applied references, and this rejection should be withdrawn.

Conclusion

The sole remaining ground for rejection having been addressed and, it is believed, overcome by the above amendments and remarks, it is respectfully requested that this rejection be withdrawn and that all claims be allowed.

EXCEPT for issue fees payable under 37 C.F.R. § 1.18, the Director is hereby authorized by this paper to charge any additional fees during the entire pendency of this application including fees due under 37 C.F.R. §§ 1.16 and 1.17 which may be required, including any required extension of time fees, or credit any overpayment to Deposit

Account 50-0310. This paragraph is intended to be a **CONSTRUCTIVE PETITION FOR EXTENSION OF TIME** in accordance with 37 C.F.R. § 1.136(a)(3).

Respectfully Submitted,
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